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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,712	STANLEY ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's arguments and amendments filed on 7/29/2010 have been entered.

2. Claims 1-40 are cancelled.

3. Claims 54-65 are new.

4. Claim 52 is amended.

5. The objection to claim 52 is withdrawn in view of Applicant's amendment.

6. Claims 41-65 are examined in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57 and 65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 57 is not supported by the originally filed claims or the instantly filed specification. The only recitation in the specification regarding RPM for centrifugation is 1500 RPM for 4 minutes at 4 degrees Celsius. If Applicant believes this rejection is in error, Applicant is invited to cite line and page number where support for claim 57 can be found.

New claim 65 is not supported by the originally filed claims or the instantly filed specification. The only recitation regarding confluency % is 60-80% as recited in Example 1. If Applicant believes this rejection is in error, Applicant is invited to cite line and page number where support for the % confluency recited in claim 65 can be found.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54, 56 and 65 are unclear. The claims recites either "growing the hESCs on a culture medium" or "hESCs grown on the culture medium", however hESC's are not grown "on" a culture medium but rather "in" a culture medium. The issue with the claims being indefinite is that the claims encompass growing hESCs on the surface of a liquid, however culture medium normally comprises cell components such as serum, growth factors and cytokines and is not considered a physical support structure in contrast to, for example, a mouse feeder layer. While claim 55 recites that the culture medium comprises mouse feeder cells and this would be necessary to "plate" the mouse feeder cells on to the surface of a tissue culture dish, the culture medium on its own does not provide the support to grow cells "on" the medium.

Example 1 (line 20) of the specification recites growing hESCs of the claimed invention "on" a mouse feeder cell layer.

Claim 58 recites the limitation "the growth factors" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 41-50 remain rejected under 35 U.S.C. 102(e) as being anticipated by Thomson et al. (US Patent 6,602,711 B1, filed 2/21/2000) for reason of record in the Non-Final Office Action mailed on 2/4/2010, pgs. 3-4 (and repeated below).

Claim 41 is drawn to a method of forming hESC aggregates using centrifugation.

Claims 42-46 limit claim 41 to dissociated hESC cells, wherein the dissociation is done with trypsin and EDTA.

Claim 50 limits claim 41 to culturing the hESC aggregates to promote growth.

The specification teaches that hESC aggregates encompass embryoid bodies (pg. 1 lines 28-34)

Regarding claims 47-49, which are drawn to centrifugation using low-attachment centrifugation plates or holding vessels, wherein said vessels are round bottom wells or conical shaped wells, these claims are given no patentable weight. It would be obvious to use said plates

or vessels as a matter of design choice and one would be motivated to use said plates or vessels since they are readily available and applicable to methods of centrifuging cells.

Regarding claim 41, Thomson teaches a method of forming ES cells aggregates by obtaining a suspension of ES cells by centrifugation (col. 4 lines 10-13). Thomson continues to teach that their ES cells encompass primate and human (col. 6 lines 11-13 and claim 10). Thomson continues to teach that aggregates of ES cells encompass embryoid bodies, which are three-dimensional ES cells aggregates that facilitate subsequent differentiation (col. 2 lines 20-23).

Regarding claims 42-46, Thomson teaches that to prior to aggregation of ES cells, they are dissociated from adhering to the substrate in clumps using a combination of trypsin and EDTA (col. 2 lines 41-62).

Regarding claim 50, Thomson teaches ES cell aggregates were plated and then seven days layer stained to confirm the existence of cells of the neural phenotype (col. 4 lines 51-53).

Thomson continues to teach that it would be desirable to differentiate hematopoietic cells from the ES cells of their invention (col. 2 lines 13-16).

Thus the cited teachings of Thomson clearly anticipate the claimed invention.

Response to Arguments

Applicant's Arguments

Applicants argue in amendment filed on 7/29/2010 that Thomson teaches a method for producing primate embryoid bodies from colonies of primate embryoid stem cells adhered to a substrate, however the adhered colonies are removed in "clumps" *via* mechanical or chemical means and then incubated under non-attachment conditions so as to facilitate the formation of embryoid bodies.

Applicants continue that Thomson makes it clear that the adhered colonies are removed from the substrate *via* mechanical or chemical means so as to keep the embryonic stem cells in clumps. Applicants continue that the chemical release step involves the use of a chemical agent such as calcium disodium EDTA or a proteinase which acts on the extracellular matrix whereas mechanical removal is achieved using a pulled glass pipette to scrape the cells from the culture plate. Applicants continue that Thomson discloses that after chemical removal of the cells from the tissue plate, the cell suspension (i. e. clump) is centrifuged for 5 minutes and resuspended in a culture media with or without serum.

Applicants continue that Thomson et al. use this particular approach for the production of primate embryoid bodies from colonies of primate embryonic stem cells for the reason explained at column 2, lines 23-43 of Thomson. Applicants continue that that Thomson teaches that human embryoid body formation using conventional murine protocols fails and goes on to state that they have learned that primate embryonic stem cells die rapidly if dispersed to single cells and attachment is prevented.

Applicants continue that Thomson teaches the importance of first aggregating cells on a substrate to form cell colonies, removing/isolating the aggregated colonies in cell clumps using mechanical or chemical means, and then incubating the cell clumps under non-attaching conditions in a (serum-free) culture media so as to produce embryoid bodies. Applicants continue that in the context of the method taught by Thomson, the centrifugation step identified by the Examiner at column 4, lines 10-13, is simply used to isolate the cell clumps removed from the substrate by chemical means, prior to the incubation step. Applicants continue that it is worth noting that after mechanical removal, no centrifugation step is involved (column 4, lines 18-19 of Thomson).

Applicants continue that the present invention teaches a completely different method for producing embryoid bodies. In reference to Example 1 at pages 21-22 of the specification, human embryonic stem cells (hESCs) are grown on mouse feeder cells to 60-80% confluency, washed and resuspended in a differentiation medium (first without, and then with, growth factors). Applicants continue that the cell suspension is then aliquoted into a low adhesion plate prior to centrifugation to form hESC aggregates. Applicants continue that as identified by the Examiner at page 3 of the Office Action, the present specification at page 1, lines 28-34, makes it clear that embryoid bodies are defined as spheroids of cellular aggregates derived from one or a number of hESCs.

Applicants continue that both claims 41 and 54 are novel over Thomson because the formation of embryoid bodies from a cell suspension is the direct result of a centrifugation step. Applicants continue that as discussed previously, the centrifugation step taught by Thomson is used to isolate the primate embryonic stem cell clumps prior to the incubation step, and it is only

during the incubation step that the embryoid bodies are formed. Applicants continue that accordingly, the centrifugation step disclosed in Thomson is not directly attributable to the formation of embryoid bodies.

Applicants continue that Thomson teaches the importance of first aggregating cells on a substrate to form cell colonies prior to the formation of embryoid bodies, however, this step is not taught in the methods of the present invention. Applicants conclude that in fact the present invention teaches the very opposite, because the resuspended hESCs are aliquoted directly into each well of a 96 well round-bottomed untreated low adhesion plate (Nunc, cat # 264122) to facilitate aggregation (page 22, lines 12-14 of the present specification).

Examiner's Response

While Thomson examples may have a different context, as Applicants argue, compared to the claimed invention, the teachings of Thomson still anticipate the claimed invention. Applicant's arguments are not commensurate in scope with the pending claims. Specifically, % confluency (see claims 56 and 65), types of medium, scientific rationale and the spirit of the claimed invention are not claim limitations. Claim 41 simply requires centrifuging a suspension of hES cells, wherein the centrifugation causes aggregation of hES cells. In this regard, the teachings of Thomson as recited above clearly anticipate the claimed invention. Applicant's arguments are not persuasive since Thomson taught, the claimed method of forming hES cell aggregates.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 41 and 50-53 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. (US Patent 6,602,711 B1, filed 2/21/2000) and Kaufman et al. (2001, PNAS, Vol. 98(19), pgs. 10716-10721) for reason of record in the Non-Final Office Action mailed on 2/4/2010, pgs. 4-6 (and repeated below).

Claim 51 is drawn to differentiating cells from hESC aggregates.

Claim 52 limits the cells of claim 51 to blood cells.

Claim 53 limits claim 51 to isolating the cultured and/or differentiated hESC's.

The specification teaches on pg. 8 lines 17-20 that "blood cells" encompass 13 different cells types found in the blood, including precursor cells. Accordingly, the teachings of Kaufman et al. are relied upon below in teaching that it would be obvious and routine to differentiate blood cells from hematopoietic stem cells which are a precursor cell to all 13 types encompassed by the claims.

Thomson teaches a method of forming ES cells aggregates by obtaining a suspension of ES cells by centrifugation (col. 4 lines 10-13). Thomson continues to teach that aggregates of ES cells encompass embryoid bodies, which are three-dimensional ES cells aggregates that facilitate subsequent differentiation (col. 2 lines 20-23). Thomson continues to teach that their ES cells

encompass primate and human (col. 6 lines 11-13 and claim 10). Thomson continues that it would be desirable to differentiate hematopoietic cells from the ES cells of their invention (col. 2 lines 13-16). Thomson does not teach the differentiation of blood cells from hES cells.

However at the time of filing the ordinary artisan would have found it routine and obvious to differentiate and isolate blood cells from hES cells.

Kaufman et al. teach a method of differentiating hematopoietic cells from human ES cells (pg. 10717 col. 2 last parag. bridge pg. 10718 col. 1) with differentiation factors (pg. 10717 col. 1 parag. 4 lines 6-10).

Kaufman teaches that cells were isolated by plucking individual colonies with a pulled Pasteur pipette (pg. 10717 col. 2 parag. 2 lines 1-3).

Kaufman concludes by teaching that "The *in vitro* differentiation of human ES cells provides an opportunity to better understand human hematopoiesis and could lead to a novel source of cells for transfusion and transplantation therapies" (Abstract last sentence).

Thus the ordinary artisan at the time of filing would have found it *prima facie* obvious to combine the teachings of Thomson regarding a method of forming hESC aggregates and desiring to differentiate hematopoietic cells from said hESC aggregates with the teachings of Kaufman regarding the differentiation of hematopoietic cells from hES cells to arrive at the claimed invention of forming blood cells from hES cells. One would have been motivated to make such a combination given the teachings of Thomson that it would be desirable to differentiate hematopoietic cells from hES cells and Kaufman teaching that the *in vitro* differentiation of hematopoietic cells from hES cells could lead to novel sources of cells for transfusion and transplantation therapies. There would have been a reasonable expectation of success that the

differentiation of hematopoietic cells from hES cells taught by Kaufman would also differentiate the hES cells of Thomson since they are the same cell type.

Thus the cited art clearly supports a case of *prima facie* obviousness.

Response to Arguments

Applicant's Arguments

Applicant's rely upon their arguments above and further add that one of ordinary skill in the art would not be motivated to combine the teaching of Thomson with Kaufman since the method taught by Thomson for producing primate EBs is quite different from the method claimed by Applicant.

Examiner's Response

As discussed above, the teachings of Thomson anticipate the claimed invention and in combination with the teachings of Kaufman motivate the ordinary artisan to make and use the invention of claims 50-53.

Claims 54, 55, 56 and 59-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (US 2002/0076747 A1, published 6/20/2002) and Thomson et al. (US Patent 6,602,711 B1, filed 2/21/2000).

Regarding claims 62-65, which are drawn to centrifugation using low-attachment centrifugation plates or holding vessels, wherein said vessels are round bottom wells or conical shaped wells, these claims are given no patentable weight. It would be obvious to use said plates

or vessels as a matter of design choice and one would be motivated to use said plates or vessels since they are readily available and applicable to methods of centrifuging cells.

Regarding claim 54, Price et al. teach a method of forming hES cell aggregates comprising:

obtaining a suspension of hES cells (pg. 12 parag. 0129);

growing the hES cells on a culture medium (pg. 12 parag. 0130 lines 1-10);

harvesting the hES cells from the medium (pg. 12 parag. 0130); and

suspending the harvested hES cells in a serum-free medium (pg. 12 parag. 0130 last four lines).

Regarding claim 55, Price teaches the mouse embryonic fibroblasts can be used to support the culture medium (pg. 8 parag. 0106).

Regarding claim 56, the ordinary artisan would find the claim method of growing the hESC's to 60-80% confluency obvious, so as to avoid differentiation of hESC aggregates into specific cell types. It was well accepted in the art at the time of filing that as hESC culture approaches 100% confluency, peripheral differentiation occurs.

Regarding claim 59, Price teaches that the hES cells were counted (pg. 13 parag. 0141 lines 1-4).

Regarding claim 60, Price teaches that the hES cells were dissociated with trypsin (pg. 12 parag. 0130).

Regarding claim 61, Price teaches that EDTA was used with trypsin (pg. 12 parag. 0129).

Price et al. do not teach centrifuging a suspension of hES cells to obtain hES cell aggregates.

However it would be routine and obvious to centrifuge a suspension of hES cells to obtain hES cell aggregates.

For example Thomson et al. teach a method of forming ES cells aggregates by obtaining a suspension of either primate or human ES cells by centrifugation (col. 4 lines 10-13). Thomson continues to teach that the ES cells can be suspended in a serum-free media without attachment factors (col. 3 lines 23-30). Thomson continues that to facilitate ES differentiation, ES cells are formed into three-dimensional ES cell aggregates prior to differentiation (col. 2 lines 13-23).

Thus at the time of filing the ordinary artisan would have found it prima facie obvious to combine the teachings of Price regarding culturing and suspension of hES cells in culture and serum-free media with the teachings of Thomson regarding obtaining hES cell aggregates using centrifugation to arrive at the claimed invention. One or ordinary skill in the art would have been motivated to form hES cell aggregates from the suspension taught by Price since Thomson teaches that hES cell aggregates are formed to facilitate differentiation. There would have been a reasonable expectation of success that the centrifugation taught by Thomson would form aggregates of the suspended hES cell taught by Price, since Thomson demonstrated that either primate or human ES cells when centrifuged will form aggregates.

Thus the cited references clearly support a *prima facie* case of obviousness.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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